DETAILED ACTION

1. In view of the Appeal Brief filed on 01/07/2008, PROSECUTION IS HEREBY REOPENED. New Grounds of Rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:
(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,
(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

However, it is noted that applicant's Appeal Brief, filed on 01/07/2008, would be considered defective, given that 37 CFR 41.37(2)(ix) requires copies of the evidence relied upon.
If prosecution would not have been reopened, a Defective Notice would have been sent instead of this Office Action.

2. Claims 1, 5-10, 17 and 19 are pending and being acted upon presently as they read on anti-gp39 /anti-CD40L antibodies in the treatment of diabetes.

Claims 2-4, 11-16, 18 and 20-21 have been canceled previously.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

The rejections of record can be found in the previous Office Actions, mailed 05/04/2006, 02/07/2007, 05/09/2007 and 09/20/2007.

4. Applicant's arguments, including those presented in the Appeal Brief, filed 01/07/2008, and the examiner's rebuttal are essentially the same of record.

New Grounds of Rejection have been set forth to provide evidence to counter applicant's assertions in conjunction with the Clark Declaration that the prior art does not render obvious the claimed methods.

Applicant continues to argue the following.

The present claims call for a method of preventing T cell mediated tissue destruction associated with type I diabetes comprising the administration of a gp39 antagonist, wherein the tissue destruction results from a T cell mediated immune reaction to an autoantigen. It is this prevention of T cell mediated tissue destruction resulting from a T cell mediated, i.e., cellular, immune reaction to an autoantigen that is not taught or suggested in either Lederman or Noelle, alone or combined. Without an express or suggested teaching of these claim limitations in the prior art references, one of skill in the art would not have considered the claimed method obvious based upon their disclosure because at the time it was not known that gp39/CD40L had any role in non-B cell mediated immune responses. Additionally, the use of a gp39 antagonist to prevent T cell mediated tissue destruction associated with type I diabetes where the tissue destruction is caused by a T cell mediated immune response to an autoantigen was an unexpected and surprising result in view of the knowledge and skill in the art at the time of the filing of the application.

To prove the state of the art and provide evidence of unexpected results, Appellant submitted the Declaration of Edward A. Clark, Ph.D. (hereafter "Clark Declaration") with the Amendment and Response dated November 6, 2006. It is respectfully submitted that the Examiner did not give adequate consideration to this evidence as it establishes that after consideration of all of the facts, the method defined in the claims on appeal would not have been obvious to a person of skill in the art.

In summary, the present claims are not obvious over the combined teachings of Lederman and Noelle because:

(1) unlike the claims on appeal which cover a method of preventing T cell mediated tissue destruction resulting from T cell mediated immune responses by administering a gp39 antagonist, Lederman teaches only the inhibition of B cell mediated immune responses by the administration of a CD40L antagonist, and teaches only a method of treating diabetes by inhibition of B cell mediated immune responses, not T cell mediated responses;

(2) Noelle teaches only the administration of a gp39 antagonist in conjunction with a antigen or antigen presenting cell to induce antigen specific T cell tolerance in an organ transplant or graft versus host disease. Unlike the claims on appeal, there is no disclosure in Noelle of the claim limitations of administering a gp39 antagonist alone to prevent T cell mediated, i.e., cellular, tissue destruction associated with type I diabetes caused by a T cell mediated immune reaction to a self antigen, independent of B cell activation;

(3) there would have been no motivation to combine Lederman and Noelle because Lederman is concerned with the use of a gp39 antagonist alone to treat B cell mediated autoimmune disorders and Noelle teaches the use of a gp39 antagonist administered with an antigen or antigen presenting cell to inhibit immune responses to donor antigens. There is no description or suggestion in Noelle to modify the method described therein to exclude the administration of donor antigen or donor antigen-expressing cells for the purpose of achieving an inhibition of a response to self, such as in autoimmune disorders. Moreover, there would have been no expectation of success in achieving the presently claimed invention by combining the teachings of Lederman and Noelle;

(4) the state and knowledge of the art in June of 1995 was such that without an express or suggested teaching of the use of a CD40L antagonist to inhibit T cell mediated immune reactions that cause T cell mediated tissue destruction associated with diabetes, one of skill in the art would not have considered the currently claimed invention obvious because it was not known that gp39/CD40L had any involvement in T cell mediated immune responses independent of B cell activation; and

(5) the ability of a gp39 antagonist to prevent T cell mediated tissue destruction associated with type I diabetes, wherein the tissue destruction results from a T cell mediated immune reaction to an autoantigen was an unexpected and surprising result in view of the state of the art in June of 1995. Additionally the superior results of the antibody 24-31 in the claimed method was also surprising and unexpected in view of the disclosure of the 5c8 antibody in Lederman.

5. Claims 1, 5-10, 17 and 19 stand rejected under 35 U.S.C.§ 103(a) as being unpatentable Lederman et al. (U.S. Patent No. 6,592,868) in view of Noelle et al. (U.S. Patent No. 5,747,037) for the reasons of record and in further evidence of Lederman et al. (U.S. Patent No. 6,403,091), Strom et al. (U.S. Patent No. 5,958,403), Armistead et al. U.S. Patent No. 5,192,773), and Rubin-Kelley et al. (U.S. Patent No. 5,571,507).

Applicant's arguments, including those presented in the Appeal Brief, filed 01/07/2008, and the examiner's rebuttal are essentially the same of record.

New Grounds of Rejection have been set forth to provide evidence to counter applicant's assertions in conjunction with the Clark Declaration that the prior art does not render obvious the claimed methods.

In contrast to applicant's continual arguments that Lederman et al., Lederman et al. teach only the inhibition of B cell mediated immune responses by the administration of a CD40L antagonist and that the state and knowledge of the art in June of 1995 did not provide an express or suggested teaching of the use of a CD40L antagonist to inhibit T cell mediated immune reactions,

Lederman et al. (U.S. Patent No. 6,403,091) claims are drawn to methods of inhibiting rejection of transplant organ with 5c8-specific antibodies.

Therefore, in addition, in Lederman et al. (U.S. Patent No. 6,592,868) claiming treatment of diabetes and other conditions associated with T cell-mediated immune responses,

Lederman et al. (6,403,091) claiming treatment of inhibiting transplant rejection reads on classic T cell responses.

It has been long-recognized (e.g., since the 1960's) by the ordinary artisan that transplant rejection occurs through cell-mediated immune responses, that is, T-cell mediated immune responses.

While B cell responses can play a role in certain aspects of transplant rejection (e.g., xenotransplanation), the ordinary artisan would have immediately envisaged that the prior art teaching of inhibiting transplant rejection read on inhibiting cell-mediated immunity, that is, T cell immunity at the time the invention was made.

In contrast to applicant's arguments in conjunction with the Clark Declaration,

the disclosure of the Lederman et al. patents drawn to inhibiting B cell activation via 5c8-/ CD40L-specific antibodies was based *upon a readout of the activity of the 5c8- / CD40L-specific antibodies and did <u>not</u> limit the Lederman et al. teachings to only inhibiting B cell responses*.

Also as noted previously, the disclosure of co-inventor Noelle et al. (U.S. Patent No. 5,747,037) describes the role of B cells as antigen-presenting cells (APCs), wherein the interaction of gp39/CD40L on a T cell and a ligand on a cell which is presenting antigen (e.g., B cells; see Cells of Induction of Antigen-Specific Tolerance on columns 9-11) to the T cells can induce antigen-specific T cell tolerance, including in the context of organ transplants as well as gp39-/CD40L-mediated interactions (see entire document, including Summary of the Invention, Detailed Description of the Invention, including Administration of Cells and gp39 Antagonists and Uses of the Method of the Invention on columns 11-13).

Therefore, Noelle et al. does not limit the prior art teachings to inhibiting only B cell immune responses.

Strom et al. teach that it was known at the time the invention was made that therapeutic strategies to treat diabetes mellitus included target T cells, including T helper cells (e.g., anti-CD4 antibodies (see Background of the Invention, including column 2, paragraph 1)

Armistead et al. teach the known role and therapeutic target of T cells, including helper T cells in the treatment of organ transplants as well as autoimmune diseases, including diabetes mellitus at the time the invention was made (see column 11, lines 35-57).

Rubin-Kelley et al. teach that it was known at diabetes mellitus was a known T cell dependent autoimmune disease and that treatment included targeting T cells, including CD4+ T cells, namely helper T cells (see Background of the Invention on column 1).

Therefore, the additional evidentiary references clearly stand for the principle that the ordinary artisan understood that diabetes mellitus was a known T cell dependent autoimmune disease and that treatment included targeting T cells, including $CD4^+$ T cells, namely helper T cells.
The prior art teachings of Lederman et al. are consistent with this principle.

Applicant's arguments have not been found persuasive for the reasons for record reiterated herein for applicant's convenience and in view of the additional evidentiary references to counter applicant's / Clark's assertions concerning the teachings of the prior art of record.

As pointed out previously, although Lederman is silent about the prevention of a T cell mediated autoimmune response associated with type I diabetes, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.
See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Applicant is reminded that U.S. patents are presumed valid by U.S. courts unless proven otherwise. See 35 U.S.C. 282.

Therefore, the following of record is essentially reiterated for applicant's convenience.

Again, applicant has argued in conjunction with the 132 Clark Declaration / Exhibits that the prior art is based upon incorrect assumptions and that methods of inhibiting T cell-mediated immune responses at the time the invention was made with gp39 antagonists lacked a reasonable expectation of success (e.g., June 1995).

Applicant also submits that the prior art, particularly Lederman et al. is limited to inhibiting humoral or B-cell mediated immune responses and that there is no functional data in Lederman assessing the role of anti-CD40L antibody in vivo which would be essential to know if the antibody could inhibit autoimmune disease.

Applicant did acknowledge that the prior art inhibited T cell – B cell interactions and that antigen-presenting cells are important in generating immune responses.
However, it appears that applicant did not mention
that B cells are important antigen-presenting cells in humans (e.g., see Noelle et al., column 10, paragraph 1);
that Noelle et al. does teach inducing T cell tolerance or non-responsiveness via gp39 antagonists;
that both Lederman et al. and Noelle et al. (co-inventor) do teach treating autoimmunity as well as other conditions associated with T cell immune responses with gp39 / CD40L / 5C8 antagonists and
that Lederman et al. teach and claim methods of treating diabetes (e.g., see Claim 7 of Lederman et al.).

Applicant's arguments, including the reliance upon the 132 Clark Declaration and Exhibits focus on mechanisms and not on the teachings of the prior art set forth in the rejection of record.
Applicant submits that it is more than a difference in mechanism of action that distinguishes the present invention over the teachings of the prior art. The treatment of "tissue damage [that] results from a T cell mediated immune reaction to an autoantigen" by a patient with type I diabetes that is called for in the present claims is different than treating tissue damage resulting from B cell mediated immune reactions. The former involves treating inflammation and destruction of beta cells by macrophages and cytotoxic T cells, while the latter involves autoantibodies. As explained by Dr. Clark, tissue damage caused by a T cell mediated immune reaction to an autoantigen was not considered treatable by gp39 antagonists in June of 1995 (e.g., see Declaration of Clark, paragraphs 14 and 16).
Applicant submits that the evidence submitted with the 04/01/2005 Reply
(Noelle Declaration (Exhibit D) and Exhibits B and C) as to the unexpected superior results of the 24-31 antibody in vivo as compared to the 5c8 antibody has not been accorded its due weight. In addition to being therapeutically safe by not causing thromboses (contrary to hu5c8), the antibodies called for in the present claims block binding of CD40 to gp39 in vivo more effectively than 5c8. This powerful objective evidence of superior results weighs heavily in favor of patentability but has been accorded little or no consideration.

In contrast to applicant's assertions,
the prior art of record is not required to provide actual efficacy for the specifically claimed methods to render the instant claims obvious.

Again, other than relying on asserted differences in mechanisms of action based upon the asserted teachings of the prior art set forth in the rejection of record and that relied upon in the 132 Declaration and Exhibits,
applicant has not distinguished between the motivation and expectation of success in treating the same patient populations, namely patients with diabetes, with the same gp39 / CD40L / 5C8 antagonists, namely gp39- / CD40L- / 5c8- specific antibodies.
Further, applicant ignores the claims of Lederman et al. (U.S. Patent No. 6,592,868).

Applicant is reminded that U.S. patents are presumed valid by U.S. courts unless proven otherwise. See 35 U.S.C. 282.

While applicant and the 132 Clark Declaration are essentially indicating the treating the T cell-mediated tissue destruction associated with type I diabetes would not have been expected at the time the invention was made and that Lederman et al. does not provide any in vitro or in vivo data to support their patent,
applicant has not addressed the presumption of validity as well as the clear teachings of the Lederman et al. patent, which includes methods of treating diabetes with gp39- / CD40L- / 5C8-specific antibodies.

While Lederman et al. tests and directs the ordinary artisan to inhibiting T cell – B cell interactions with 5c8 (i.e., gp39 / CD40L) antagonists, including inhibiting humoral immune responses,
Lederman et al. is not is limited as asserted by applicant and the 132 Clark Declaration. As indicated previously, Lederman et al. do teach treating diseases and conditions associated with T cell mediated immune responses.

Even applicant and the 132 Clark Declaration note that most of the diseases listed by the prior art are primary B cell-mediated, thereby acknowledging that the prior art targeted diseases also including T cell-mediated immune responses as well.
While applicant asserts that the teachings of Noelle concerning the use of gp39 antagonists in the treatment of pancreatic allografts would not suggest treating the underlying disease of such treatment, namely diabetes.

Again, applicant appears to ignore or to dismiss the teachings of instant co-inventor's own prior art disclosure of treating autoimmunity with gp39-specific / CD40L-specific antibodies (e.g., see IV. Uses of the Method of the Invention on column 13) in addition to inducing antigen-specific unresponsiveness or tolerance (e.g., see Summary of the Invention and Detailed Description of the Invention).
It appears that applicant is making statements against their own interest.

Applicant's assertions of unexpected results do not overcome clear evidence of obviousness of treating patients with diabetes with anti-CD40 ligand antibodies, including the 24-31 antibody at the time the invention was made

As pointed out previously, although Lederman is silent about the prevention of a T cell mediated autoimmune response associated with type I diabetes, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.
See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

"{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable. "In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

As noted previously, although the 5c8 antibody and the instant 24-31 antibody epitope specificities nor describe "T cell mediated autoimmune responses" per se,
the prior art , including both Lederman et al. and Noelle et al. clearly provided for inhibiting cell-mediated inflammatory conditions, autoimmunity or diabetes at the time the invention was made with 5C8-specific / CD40L-specific antibodies.

In contrast to applicant's assertions,
the prior art teaching of Lederman et al. is not limited to treating B cell immune responses only, given its teaching of inhibiting transplant rejection and autoimmune diseases such as diabetes.

Although applicant has argued that there is no suggestion in the '037 in merely administering the gp39 antagonist without antigen,
Lederman et al. does teach treating diabetes with 5c8- (gp39-, CD40 ligand-) specific antibodies in the absence of antigen presenting cells.

In addition, autoimmunity by its very nature encompasses the presence of autoantigen.

'037 provides for a more efficient method for inducing long term specific nonresponsiveness to autoantigens by providing antigen presenting cells in methods to treat an autoimmune condition such as diabetes, already taught to be treated with CD40 ligand-specific antibodies in the absence of antigen presenting cells by Lederman et al.

Further, it has been noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.

Given the assertions of unexpected results, the prior art already provides clear direction in providing for the particular 24-31 CD40 ligand-specific antibody in the treatment of diabetes at the time the invention was made. In this case the teachings of both the primary and second references indicate success in treating diabetic patients with anti-CD40 ligand antibodies in the face of having to solve the same or nearly the same problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to treat the same or nearly the same diabetic patient populations with antagonistic therapeutic anti-CD40 ligand antibodies to dampen the well known inflammatory problems associated with diabetic patients in the art.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Given the antagonistic properties of the particular 24-31 and 89-76 CD40L-specific antibodies taught by Noelle et al. ('037), the ordinary artisan would have been motivated to substitute these CD40L antagonists into the methods of treating autoimmune diseases such as diabetes, as taught by Lederman, given their inhibitory properties were consistent with the antagonistic CD40L-specific antibodies taught by the prior art. Noelle et al. ('037) and Lederman et al. all teach the advantages of anti-CD40L antibodies to inhibit immune responses by targeting the CD40L on T helper cells in therapeutic modalities of immunosuppression at the time the invention was made. Applicant's arguments that the prior art, including Lederman et al. are only limited to treating B cell immune response only is not consistent with the a reasonable interpretation of the prior art in the applicability of CD40L-specific antibodies in the treatment of various inflammatory or immune regulated conditions and disorders, including diabetes itself.

While the prior art anti-CD40L antibodies may have been tested with respect to parameters associated with B cell activation and immunoglobulin production, the prior art clearly teaches that CD40L was expressed on important activated CD4+ T cells that regulated various immune responses and that CD40L was targeted in conditions and disorders known to be cell-mediated at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to treat patients with diabetes with CD40L-specific antibodies, incorporating CD40L-specific antibodies in therapeutic regimens with diabetic patients would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such methods that would have resulted in "preventing T cell-mediated destruction associated with type I diabetes with prophylactically effective amounts of antagonistic CD40L-specific antibodies, including the reference anti-gp39 / anti-CD40L 24-31 antibody" at the time the invention was made.

Applicant's arguments are not found persuasive.

7. No claim allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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